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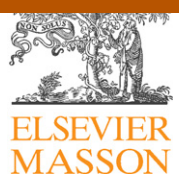

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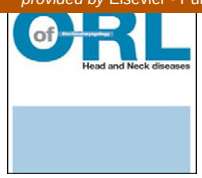

ORIGINAL ARTICLE

Clinical and histological prognostic factors in locally advanced oral cavity cancers treated with primary surgery

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KEYWORDS
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Summary
Objective: The primary objective of this study was to determine the clinical and pathological prognostic factors in locally advanced oral cavity cancers treated by primary surgery.
Methods: All patients treated by primary surgery with free-flap reconstruction for locally advanced oral cavity squamous cell carcinoma in our institution between 2000 and 2010 were included in this retrospective study. Overall, cause-specific and locoregional disease-free survivals were determined by Kaplan-Meier analyses. Clinical and histological prognostic factors were assessed by univariate (Log Rank tests) and multivariate (Cox models) analyses.
Results: A total of 149 patients (102 men and 47 women; mean age = 61.3 ± 12.1 years) were included in the study. Five-year overall, cause-specific and locoregional disease-free survivals were 55%, 68% and 71%, respectively. Age, comorbidity and tumour size (histological evaluation) were significantly correlated with overall survival ($P < 0.05$). Age, tumour size, bone invasion and surgical margins were significantly correlated with locoregional disease-free survival ($P < 0.05$).

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Conclusion: The main prognostic factors identified in this study were clinical (age and comorbidity) and histological (pathological tumour size, bone invasion and surgical margins).

Introduction

Oral cavity cancers belong to the group of upper aerodigestive tract (UADT) tumours, which represent the sixth most common form of cancer in France [1]. Surgery, when possible, remains the reference first-line treatment for oral cavity cancer. For locally advanced tumours, surgery is followed by radiotherapy, possibly in combination with concomitant chemotherapy. Surgery for oral cavity cancer comprises often-complex reconstruction techniques with extensive use of free flaps [2,3]. Many clinical, histological or biological prognostic factors have been studied, but the respective role of the various factors in clinical practice has yet to be determined. As a result of progress in surgery (resection and reconstruction techniques) and postoperative treatment (refined irradiation techniques, combination with concomitant chemotherapy), the results of treatment in terms of cancer control now need to be revised.

The primary objective of this study was to determine the clinical and histological prognostic factors of locally advanced oral cavity cancer treated by primary surgery. The secondary objectives were to analyse the cancer control results obtained and to compare them to data reported in the literature.

Materials and methods

A retrospective study was conducted on all patients treated in our institution, between 1st January 2000 and 30 June 2010. Inclusion criteria were: patients with locally advanced (stage III or IV nonmetastatic) oral cavity squamous cell carcinoma treated by primary surgery including free flap reconstruction, with no previous treatment for this tumour. Exclusion criteria were: early tumour (stage I or II), another histological type of tumour or a tumour not involving the oral cavity, recurrent tumour after previous treatment.

Tumour stage was evaluated according to the International Union Against Cancer (UICC) 2002 tumour, node, metastasis (TNM) classification. Patient comorbidity was assessed by using the Kaplan-Feinstein index (KFI) [4].

Patients included in this series were followed after treatment according to the guidelines published by the French ENT Society for the surveillance of patients treated for upper aerodigestive tract cancer [5].

The following clinical and histological data were retrieved by retrospective analysis of the patients' computerized medical files:

- clinical data: gender, age, comorbidity, tumour site, TNM stage, postoperative radiotherapy, development of tumour recurrence, patient's status at the time of the study (alive, dead, cause of death);
- histological data: tumour size (maximum diameter), depth of invasion, presence of vascular embolus and perineural invasion, bone invasion, tumour differentiation, cervical lymph node invasion (number of lymph nodes invaded, lymph node sectors invaded, presence of capsular effraction), surgical margins on the specimen, final surgical margins (after possible complementary resection and re-excision), safety margins greater than or less than 5 mm.

Overall, cause-specific and locoregional recurrence-free survivals were calculated by the Kaplan-Meier method. The impact of clinical factors (age, gender, comorbidity, T stage, N stage, global stage) and histological factors (tumour size, depth of invasion, presence of vascular embolus and perineural invasion, bone invasion, tumour differentiation, number and site of any cervical lymph node metastases, presence of capsular effraction, surgical margins and safety margins), on overall, cause-specific and locoregional recurrence-free survivals was studied by univariate analysis (Log Rank tests) followed by multivariate analysis (Cox models). All variables associated with $P < 0.10$ on univariate analysis were entered into the multivariate analysis. All statistical tests were performed with R.2.10.1 for Windows software, with a limit of significance of 5%.

Results

Patient characteristics

A total of 149 patients (102 men (68%) and 47 women (31%), with a mean age of 61.3 ± 12.1 years) were included in this study. The patient distribution according to 4 increasing comorbidity scores (Kaplan-Feinstein Index [KFI]) was as follows: KFI = 0:43, KFI = 1:63, KFI = 2:36, KFI = 3:7 patients. Cervical lymph node dissection was performed in 147 patients (85 unilateral lymph node dissections and 62 bilateral lymph node dissections). Free flap reconstruction surgery used a forearm fasciocutaneous flap ($n = 90$), lateral thigh fasciocutaneous flap ($n = 3$), osteocutaneous fibula flap ($n = 47$), osteocutaneous scapula flap ($n = 2$) or a combination of osteocutaneous fibula flap and forearm fasciocutaneous flap ($n = 7$). Postoperatively, 60 patients received exclusive radiotherapy and 58 received concomitant platinum-based chemoradiotherapy. Thirty-one patients were therefore treated by surgery alone without adjuvant radiotherapy.

Mean tumour size (maximum diameter) measured on histological sections was 34.6 ± 15.6 mm and mean depth of invasion was 19.2 ± 10.4 mm. The mean number of lymph node metastases detected in cervical lymph node dissections was 1.6 ± 2.2, with capsular effraction in a mean of 0.6 ± 1.2 nodes. Histologically confirmed lymph node invasion was

Table 1 Clinical and histological characteristics of 149 patients operated for locally advanced oral cavity cancer.

Characteristics	$n = 149$	Percentage
Gender: female/male	47/102	32/68
Age: > 70 years/ < 70 years	40/109	27/73
Comorbidity KFI < 2/KFI ≥ 2	106/43	71/29
T Stage		
T2	11	7
T3	39	26
T4	99	67
Stage N		
N0	80	54
N1	25	17
N2a, b or c	40	27
N3	4	3
Global tumour stage: III/IV	27/122	18/82
Bone invasion	68	46
Perineural invasion	24	16
Vascular emboli	8	5
Tumour differentiation		
Well differentiated	89	60
Moderately differentiated	36	24
Poorly differentiated	24	16
Depth of tumour invasion		
< 20 mm	104	70
> 20 mm	45	30
Lymph node invasion	94	64
Capsular effraction	51	35
Positive surgical margins	25	17
Positive final surgical margins	5	4
Safety margin > 5 mm	91	61

KFI: Kaplan-Feinstein Comorbidity Index.

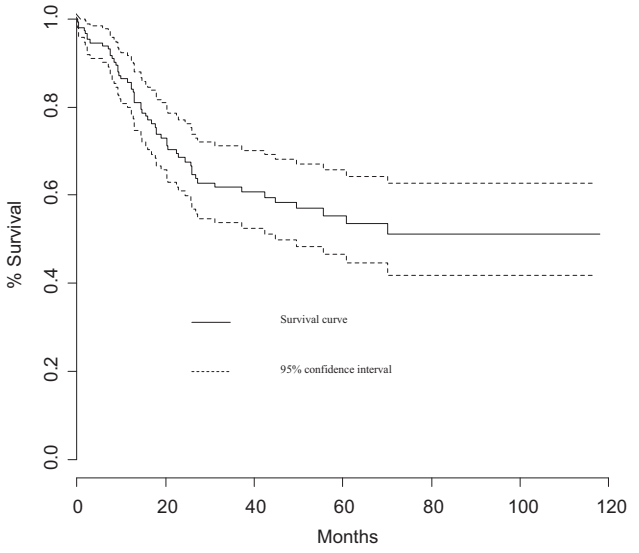
observed in the following cervical node sectors: IA: five cases, Ib: 36 cases, IIA: 58 cases, IIB: 11 cases, III: 32 cases, IV: five cases, V: one case. Clinical and histological characteristics of the patients of this study are shown in Table 1.

Survival and prognostic factors

Median follow-up in this study was 47.7 months. At the end of this follow-up, 46 patients presented tumour recurrence, including 28 locoregional recurrences, nine metastatic recurrences and nine combined locoregional and metastatic recurrences. These recurrences occurred after a mean interval of 15.6 ± 11.8 months.

Overall survival

Two, 3- and 5-year overall survival was 69%, 62% and 55%, respectively. On univariate analysis, age (> 70 years; $P = 0.01$), comorbidity (KFI 2; $P < 0.0001$), tumour size (> 30 mm; $P = 0.03$) and presence of lymphadenopathy with capsular effraction ($P = 0.02$) had a statistically significant negative impact on overall survival. The prognostic role of age ($P = 0.03$), comorbidity ($P = 0.0002$) and tumour size ($P = 0.02$) was confirmed on multivariate analysis. In contrast, the influence of lymphadenopathy with capsular effraction on overall survival was not confirmed on multivariate analysis.



time (months)	0	20	40	60	80	100
n.risk	149	85	54	32	15	3
n.event	0	36	13	4	2	0
survival	1	0.73	0.61	0.55	0.51	0.51

Figure 1 Overall survival curve for 149 patients operated for locally advanced oral cancer.

Fig. 1 shows the overall survival curve for all patients.

Cause-specific survival

Two, three- and five-year cause-specific survival was 77%, 73% and 68%, respectively. In univariate analysis, age (> 70 years; $P = 0.05$), comorbidity (KFI 2; $P = 0.002$) and tumour size (> 30 mm; $P = 0.007$) had a statistically significant negative impact on cause-specific survival. These results were confirmed on multivariate analysis (age: $P = 0.03$; comorbidity: $P = 0.02$; tumour size: $P = 0.006$).

Locoregional recurrence-free survival

Two, three- and five-year locoregional recurrence-free survival was 77%, 73% and 71%, respectively. On univariate analysis, age (> 70 years; $P = 0.02$), comorbidity (KFI 2; $P = 0.01$), tumour size (> 30 mm; $P = 0.02$), bone invasion ($P = 0.02$), final surgical margins (positive margins; $P = 0.04$) and safety margins (< 5 mm; $P < 0.04$) had a statistically significant negative impact on locoregional recurrence-free survival. On multivariate analysis, only the patient's age ($P = 0.001$), tumour size ($P = 0.002$), bone invasion ($P = 0.04$) and final surgical margins ($P = 0.01$) still had a statistically significant impact on locoregional recurrence-free survival.

Histological and clinical prognostic factors are shown in Tables 2 and 3.

Table 2 Clinical prognostic factors in patients operated for locally advanced oral cavity squamous cell carcinoma.

Clinical parameters	Overall survival	Cause-specific survival	Locoregional recurrence-free survival
	P (UA)/(MA)	*P* (UA)/(MA)	*P* (UA)/(MA)
Age	0.01/0.03	0.05/0.03	0.02/0.001
Gender	0.32/—	0.59/—	0.24/—
Comorbidity	< 0.0001/0.0002	0.002/0.02	0.01/0.14
Adjuvant radiotherapy	0.61/—	0.55/—	0.69/—
T stage	0.45/—	0.42/—	0.41/—
N stage	0.25/—	0.16/—	0.51/—

P (UA): p value on univariate analysis (Log Rank tests); *P* (MA): p value on multivariate analysis (Cox models). All variables associated with $P < 0.10$ on univariate analysis were entered into Cox models.
Age: > 70 years versus < 70 years; comorbidity (KFI: Kaplan-Feinstein index): KFI 2 versus KFI < 2; stage T: T2 or T3 versus T4; stage N: N ≥ 1 versus N0.

Table 3 Histological prognostic factors in patients operated for locally advanced oral cavity squamous cell carcinoma.

Histological parameters	Overall survival	Cause-specific survival	Locoregional recurrence-free survival
	P (UA)/(MA)	*P* (UA)/(MA)	*P* (UA)/(MA)
Tumour size	0.03/0.02	0.007/0.006	0.02/0.002
Depth of tumour invasion	0.08/[a]	0.09/[a]	0.17/—
Bone invasion	0.31/—	0.13/—	0.02/0.04
Perineural invasion	0.82/—	0.31/—	0.2/—
Vascular emboli	0.48/—	0.89/—	0.45/—
Tumour differentiation	0.40/—	0.26/—	0.19/—
Lymph node invasion	0.25/—	0.16/—	0.5/—
Capsular effraction	0.02/0.11	0.12/—	0.88/—
Surgical margins	0.78/—	0.4/—	0.13/—
Final surgical margins	0.92/—	0.49/—	0.04/0.01
Safety margins	0.2/—	0.55/—	0.04/0.3

P (UA): *P* (UA): *P* value on univariate analysis (Log Rank tests); *P* (MA): p value on multivariate analysis (Cox models). All variables associated with $P < 0.10$ on univariate analysis were entered into Cox models.
Tumour size: maximum diameter > 30 mm versus ≤ 30 mm; tumour invasion: depth of invasion > 20 mm versus ≤ 20 mm; safety margins ≥ 5 mm versus < 5 mm.
[a] Parameter eliminated from multivariate analysis as it was too closely related to tumour size.

Discussion

This study was based on a large, homogeneous patient series, as all patients included in this study had locally advanced oral cavity squamous cell carcinoma treated by primary surgery. The treatment of oral cavity cancers is surgical. In addition to the usual clinical prognostic factors, histological data are used to determine the indications for adjuvant therapy. As clearly illustrated by this series, the majority of patients with locally advanced oral cavity cancer were treated by adjuvant radiotherapy often potentiated by a platinum salt. Several patients can nevertheless be effectively treated by surgery alone, after wide resection and in the absence of any poor prognostic factors.

Surgery for locally advanced oral cavity cancer involves complex reconstruction techniques. The present series reflects the practice reported by most authors, as the forearm fasciocutaneous flap is the flap most commonly used for repair of extensive mucosal and muscle defects of the oropharyngeal region, while the osteocutaneous fibula flap is the flap most commonly used for mandibular reconstruction [3,6—9].

In the current context of rapid growth of concomitant chemoradiotherapy protocols for the treatment of

Table 4 Survival rates recently published in the literature compared to those of this study.

Studies	Survival rates	Comments
Our study	5-year OS = 55% (stages III and IV) 5-year CSS = 68%	Retrospective study, primary surgery
Blanchard et al., 2011. [10]	5-year OS = 33% (stage III and IV)	Meta-analysis, operated and non-operated patients
Kang et al. in press [11]	5-year CSS = 63% (stage IV) 5-year OS = 55% (all T, pN +)	Retrospective study, well differentiated squamous cell carcinomas, primary surgery
Arduino et al. 2008. [12]	5-year OS = 52% (T4)	Retrospective study, operated (88%) and non-operated patients
Jan et al. 2011. [13]	5-year OS = 69% (stage III) 5-year OS = 53% (stage IV)	Retrospective study, operated (95%) and non-operated patients
Garzino-Demo et al. 2006 [14]	3-year OS = 49% (stage III and IV)	Retrospective study, primary surgery
Husseiny et al. 2000 [15]	5-year OS = 65% (stage I to IV)	Retrospective study, operated (86%) and non-operated patients
Choi et al. 2006 [16]	5-year OS = 51% (stage IV)	Retrospective study, operated (76%) and non-operated patients

OS: overall survival; CSS: cause-specific survival.

upper aerodigestive tract tumours, it seemed interesting to present the recent cancer control results of primary surgery in locally advanced oral cavity cancer, in which treatment remains essentially surgical [2]. The median follow-up in this study, almost 4 years, was suitable for analysis of survival and prognostic factors, as tumour recurrences occurred after a mean interval of about 15 months. The survival rates reported in this study, comprising more than 80% of patients with a stage IV tumour, appear to be satisfactory, particularly for 5-year cause-specific and locoregional recurrence-free survivals (68% and 71%, respectively). Local disease progression can therefore be avoided in more than two-thirds of patients. This result must be emphasized in view of the major impact of local recurrence on the patient's quality of life. The survival rates reported in this study are consistent with those reported in recent studies (Table 4) [10—16].

Advanced age and high comorbidity appeared to be the main clinical prognostic factors in this study, as also reported by many authors for various upper aerodigestive tract tumour sites, whether or not the primary treatment was surgery [17—20], as elderly patients or patients in poor general health are more vulnerable to progression of disease and often require simplification of the treatment sequence (frequent contraindications to adjuvant concomitant chemotherapy). Tumour stage was not identified as a prognostic factor in this study, which can be explained by the homogeneity of the study population in terms of initial extent of the disease. No prognostic impact of tumour stage was demonstrated in this study, as all patients presented locally advanced tumour.

The main histological prognostic factor was the maximum tumour diameter. This may appear to be somewhat surprising, as tumour size is one of the main determinants of T stage, which did not have any prognostic impact in this study. However, in addition to tumour size, T stage also takes into account invasion of certain structures such as the mandible or extrinsic muscles of the tongue. Clinical evaluation of T stage may also be subject to relatively marked interindividual variation. Precise measurement of maximum tumour diameter on histological sections therefore appears to be a more relevant prognostic factor than T stage. The depth of tumour invasion tended to have a prognostic impact, but was not statistically significant. The presence of bone invasion and the surgical margin status (final margins after possible complementary resection and re-excision) had a negative impact on prognosis, and more specifically on locoregional recurrence-free survival, emphasizing the importance of the quality of surgical resection in terms of prognosis. Primary surgery is only indicated for the treatment of upper aerodigestive tract tumours if it allows complete resection of the primary tumour. In the present study, surgical margins were considered to be negative for 96% of patients. Some histological factors usually shown to have a prognostic impact in oral cavity cancer were not confirmed by this study [11—13]. For example, the poorly differentiated nature of the tumour, the presence of perineural invasion, vascular emboli, cervical lymph node metastases or capsular effraction were not identified as prognostic factors in this study. In a recent study based on 467 patients with oral cavity squamous cell carcinoma, Kang et al. demonstrated the major prognostic impact of depth of tumour invasion and cervical lymph node invasion (more than two lymph nodes invaded, invasion of levels IV and V) [11]. In another recent study, Jan et al. demonstrated the prognostic impact of surgical margins, as well as the prognostic impact of tumour stage and capsular effraction on cervical lymphadenopathies [13].

Conclusion

In this study, primary surgery for locally advanced oral cavity cancer achieved 5-year local control in more than 70% of cases. The main clinical prognostic factors were age and comorbidity. In contrast with T stage, tumour size measured on histological sections was identified as one of the main prognostic factors. Bone invasion and surgical margins were the other two histological parameters with a pejorative impact on prognosis.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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